

## **DETAILED ACTION**

### ***Response to Amendments***

Applicant's amendments filed 8/4/09 to claims 1-6, 10m 11m and 13-17 have been entered. No claims have been canceled or added in this reply. Claims 1-41 remain pending in the current application, of which claims 1-17 are being considered on their merits. Claims 18-41 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

### ***Election/Restrictions***

Applicant's election of the species "treatment with immobilized endocrine growth factors" in the reply filed on 7/11/08 is still in effect over the claims.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 requires obtaining pluripotent stem cells that "form organoid bodies," then cultivating the stem cells to generate hormone-producing cells, which is confusing because the relevance of the organoid body formation is unclear. This is further

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complicated by the presence of claims 2-5, which describe various embodiments in which different versions of the cells are cultured. Clarification is required.

Because claims 2-17 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

It is not clear how claim 2 further limits claim 1, since claim 1 requires that the stem cells be cultivated and differentiated. Clarification is required.

Claim 8 refers to "cellular imprinting," which is queried. Generally, in cell biology, "imprinting" refers to epigenetic gene control in which certain nucleotides in a cell's DNA are modified, e.g. with a methyl group. The term "imprinting" is discussed at page 3, line 27, et seq. in general and confusing terms. "Imprinting" appears to be synonymous with "treatment with growth and differentiation factors." Applicant fails to provide a sufficiently limiting definition as to allow this non-art term to be used in the claims. Clarification is required. Applicant refers to the same paragraph and makes a general allegation that the meaning of the term is clear, but this urging is not supported by declarations of skilled artisans or even by the provision of a published document that employs the term in the same manner used by applicants. The arguments at page 11 amount to a *per se* allegation of patentability and are unpersuasive.

Claim 12 requires that "non-identified and selected cells" be subjected to further processes, but it is not clear whether this claim intends to imply that these cells should also be stimulated to form hormone-producing cells or whether they should be employed in some unnamed downstream application. Clarification is required.

Claim 16 requires that the mammalian stem cells be isolated from a vertebrate, but this limitation does not appear to further limit claim 1, since all mammals are vertebrates. Clarification is required.

***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 10, and 12-16 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zulewski et al. (2001, *Diabetes* 50: 521-533; reference U). The claims are interpreted as being drawn to a method for generating mammalian cells producing pancreatic hormone, the method comprising obtaining pluripotent stem cells from exocrine glandular tissue of a mammal, allowing the cells to form organoid bodies, and differentiating the cells in the organoid bodies into mammalian cells producing pancreatic hormone. In some dependent claims, the differentiating step comprises stimulating the yielded pancreatic hormone-secreting cells with an immobilized differentiation factor in the culture medium. In some dependent claims, the stem cells are obtained from pancreatic tissue.

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Zulewski teaches obtaining islets from rat pancreases, then culturing them on plates coated with concanavalin A (conA) and selecting those cells that do not adhere to the plates. See page 525, column 1, under "Isolation and proliferation of NIP cells in vitro." Zulewski teaches culturing these non-adherent cells in medium containing bFGF and EGF to yield nestin-positive islet-derived progenitor (NIP) cells. See page 522 under "Isolation and culture of pancreatic islets." Zulewski teaches that NIP cells form spherical clusters (SCs) when cultured for several days and that these SCs spontaneously express the pancreatic genes NCAM and CK19. See page 525, column 2. Zulewski further teaches that the differentiated NIPs secrete insulin and glucagon. See page 528, column 2, under "Discussion." Zulewski postulates that the NIPs are multipotential stem cells. See page 528, column 2, under "Discussion," and page 530, last paragraph.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' stem cell differs, and if so to what extent, from the NIP cells discussed in Zulewski and used in Zulewski's method for making cells that produce pancreatic hormones. Both the instant cells and Zulewski's NIP cells are obtained from adult pancreatic islet tissue. Zulewski's NIP cell expresses nestin, as do the instant cells. See the declaration under 37 C.F.R. 1.132 by inventor Kruse at section 8. Both applicant's stem cell and Zulewski's NIP cells form aggregates *in vitro* (the "spherical clusters" of Zulewski appear to be identical to the "organoid bodies" disclosed by applicant). The cited art taken as a whole demonstrates a reasonable probability that the NIP cells of the prior art is either identical or sufficiently similar to the

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stem cells used in applicant's method that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

The mere fact that a characteristic of NIP cells is not disclosed in a reference does not make methods of using them patentable. NIP cells possess inherent characteristics which might not be displayed in the tests used in Zulewski. Clear evidence that the NIP cells of the cited prior art do not possess a critical characteristic that is possessed by applicants' stem cells (for example, the ability to yield cells from all three embryonic germ layers or the expression of some marker) would advance prosecution and might permit allowance of claims to applicants' method.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zulewski et al. (2001, *Diabetes* 50: 521-533).

The teachings of Zulewski are relied upon as above. Zulewski does not exemplify a method in which the NIP cells are obtained from a primate, but Zulewski does envision isolating islet cells from human patients and culturing those islets as disclosed in the working embodiment to yield cells to treat the patients. See page 531, column 2, last paragraph.

A person of ordinary skill in the art would have had a reasonable expectation of success in carrying out the method of Zulewski with stem cells isolated from a primate, for example a human, because Zulewski specifically suggests that the method could be applied to such cells. The skilled artisan would have been motivated to substitute

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human islets for rat islets in Zulewski's method in order to yield human cells useful for treating human patients.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to obtain stem cells from human pancreas tissue and culture them as taught by Zulewski to yield pancreatic hormone-producing cells because Zulewski explicitly suggests such a method.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 6-9 are is rejected under 35 U.S.C. 103(a) as being unpatentable over Zulewski as applied to claims 1-5, 10, and 12-16 above, and further in view of Armstrong (1998, U.S. Patent 5,830,507; reference A).

The teachings of Zulewski are relied upon as above. Zulewski does not exemplify a method in which EGF and bFGF are immobilized on a substrate when they are supplied to the stem cells.

Armstrong teaches culturing cells on microspheres *in vitro*. See column 4, lines 15-19. Armstrong teaches that any growth factor, including EGF and bFGF, may be immobilized onto the surface of the microspheres and that the microspheres may be modified to effect controlled delivery of the growth factor. See column 12, lines 51-64.

A person of ordinary skill in the art would have had a reasonable expectation of success in delivering the EGF and bFGF in the method of Zulewski using the growth factor-coated microspheres of Armstrong because Armstrong teaches that such

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microspheres are useful for providing growth factors to cells *in vitro*. The skilled artisan would have been motivated to select the growth factor-coated microspheres of Armstrong because Armstrong teaches that they provide controlled delivery of the factors.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zulewski as applied to claims 1-5, 10, and 12-16 above, and further in view of Laurance et al. (1998, U.S. Patent 5,712,159; reference B).

The teachings of Zulewski are relied upon as above. Zulewski does not exemplify a method in which the pancreatic hormone-producing cells are selected using a cell sorting process.

Laurance teaches a method for sorting pancreatic beta cells, which produce pancreatic hormone, from other pancreatic tissue by carrying out fluorescence-activated cell sorting (FACS) with a monoclonal antibody against islet cells. See column 1, line 46, through column 2, line 9.

A person of ordinary skill in the art would have had a reasonable expectation of success in using the sorting method of Laurance to remove the pancreatic hormone-producing cells yielded by the method of Zulewski from other cells in the culture because Laurance teaches that monoclonal antibodies may be used to sort pancreatic hormone-producing cells from contaminating cell types. The skilled artisan would have

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been motivated to isolate the hormone-producing cells because Zulewski envisions a therapeutic application for them, so one would have desired to administer only the hormone-producing cells to patients.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to sort the cells yielded by Zulewski's method with the sorting method of Laurance because Laurance and Zulewski both suggest the desirability of isolating these useful cells for treating patients.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

### ***Response to Arguments***

Applicant's comments regarding the enablement and written description rejections have been considered to the extent they read on the above art rejection, but they are not persuasive of error. Applicant supplies a declaration under 37 C.F.R. 1.132 by inventor Kruse (hereafter "the Kruse declaration"), which establishes that the cells that serve as starting material for the instant method are stem cells because they express nestin, a stem cell marker. Applicant's comments appear to support the examiner's holding of obviousness, since at page 8 of the reply, applicants state that the person of ordinary skill in the art could determine "appropriate solution conditions to practice the claimed process, without undue experimentation."

***No claims are allowed. No claims are free of the art.***

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

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714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/  
Primary Examiner, Art Unit 1651